

PubMed Nucleotide Protein Genome Structure PopSet Taxonomy OMIM

Search PubMed for

Display Abstract Sort Save Text Add to Clipboard

Show: Items 1-20 of 44 Page 1 of 3

About Entrez

Entrez PubMed
Overview
Help | FAQ
Tutorial
New/Noteworthy

PubMed Services
Journal Browser
MeSH Browser
Single Citation Matcher
Batch Citation Matcher
Clinical Queries
Cubby

Related Resources
Order Documents
NLM Gateway
Consumer Health
Clinical Alerts
ClinicalTrials.gov
PubMed Central

Privacy Policy

☐ 1: Growth Factors 2001;18(4):251-9

GDF-8 propeptide binds to GDF-8 and antagonizes biological : inhibiting GDF-8 receptor binding.

Thies RS, Chen T, Davies MV, Tomkinson KN, Pearson AA, Shakey Q NM.

Genetics Institute, Inc., Cambridge, MA 02140, USA. sthies@genetics.com

GDF-8 is a new member of the TGF-beta superfamily which appears to be a regulator of skeletal muscle mass. Factors which regulate the biological activity of GDF-8 have not yet been identified. However, the biological activities of TGF-beta superfamily members, TGF-beta1, -beta2 and -beta3, can be inhibited by noncovalent association with TGF-beta1, -beta2 and beta3 propeptides cleaved from the C-termini of the TGF-beta precursor proteins. In contrast, the propeptides of other beta superfamily members do not appear to be inhibitory. In this investigation we demonstrate that purified recombinant GDF-8 propeptide associates with and inhibits recombinant GDF-8 to form a noncovalent complex, as evidenced by size exclusion chromatography and chemical crosslinking analysis. Furthermore, we show that GDF-8 propeptide inhibits the biological activity of GDF-8 assayed on A204 rhabdomyosarcoma cells transfected with a (CAGA)₁₂ reporter construct. We demonstrate that GDF-8 propeptide inhibits specific GDF-8 binding to L6 rhabdomyosarcoma cells. Collectively, these data identify the GDF-8 propeptide as an inhibitor of GDF-8 biological activity.

PMID: 11519824 [PubMed - in process]

☐ 2: Proc Natl Acad Sci U S A 2001 Apr 24;98
(9):5104-9

Related Articles, Nucleotide, OMIM

Full text article at
www.pnas.org

PubMed Central
access FREE full text articles

**Mutation in bone morphogenetic protein receptor-IB is associated with
increased ovulation rate in Booroola Merino ewes.**

Mulsant P, Lecerf F, Fabre S, Schibler L, Monget P, Lanneluc I, Pissel J, Monniaux D, Callebaut I, Cribiu E, Thimonier J, Teyssier J, Bodin I, Chitour N, Elsen JM.

Institut National de la Recherche Agronomique, Laboratoire de Genetique (BP, 27, 31326 Castanet-Tolosan, France. mulsant@toulouse.inra.fr

Ewes from the Booroola strain of Australian Merino sheep are characterized by a high ovulation rate and litter size. This phenotype is due to the action of the *FecB* a major gene named *FecB*, as determined by statistical analysis of phenotypic and genetic analysis of 31 informative half-sib families from heterozygous sires that the *FecB* locus is situated in the region of ovine chromosome 6 corresponding to human chromosome 4q22-23 that contains the bone morphogenetic protein (*BMPR-IB*) gene encoding a member of the transforming growth factor-beta receptor family. A nonconservative substitution (Q249R) in the *BMPR-IB* cDNA sequence was found to be associated fully with the hyperprolificacy phenotype of Booroola ewes. In vitro, ovarian granulosa cells from *FecB(B)/FecB(B)* ewes were more responsive than granulosa cells from *FecB(+)/FecB(+)* ewes to the inhibitory effect of the steroidogenesis of GDF-5 and BMP-4, natural ligands of *BMPR-IB*. It is suggested that in *FecB(B)/FecB(B)* ewes, *BMPR-IB* would be inactivated partially, leading to an advanced differentiation of granulosa cells and an advanced maturation of oocytes.

PMID: 11320249 [PubMed - indexed for MEDLINE]

☐ 3: J Neural Transm Suppl 2000;(60):273-6

Related

GDF-15/MIC-1 a novel member of the TGF-beta superfamily.

Strelau J, Bottner M, Lingor P, Suter-Crazzolara C, Galter D, Jaszai J, Schober A, Kriegelstein K, Unsicker K.

Neuroanatomy and Center for Neuroscience, University of Heidelberg, Federal Republic of Germany.

We have cloned, expressed, and raised antibodies against a novel member of the TGF-beta superfamily, growth/differentiation factor-15 (GDF-15). The predicted protein is identical to macrophage inhibitory cytokine-1 (MIC-1), which was discovered simultaneously. GDF-15 is a more distant member of the TGF-beta superfamily and does not belong to one of the known TGF-beta subfamilies. In the CNS, GDF-15 mRNA is abundantly expressed by the choroid plexus. In addition we have evidence that GDF-15/MIC-1 is a potent trophic factor for selected classes of neurons in vitro and in vivo. Thus, GDF-15 is a novel neurotrophic factor with prospective treatment of disorders of the CNS.

Publication Types:

- Review
- Review, tutorial

PMID: 11205146 [PubMed - indexed for MEDLINE]

□ 4: Ann N Y Acad Sci 2000;919:86-96

Relate

Mechanisms of cell transformation in the Syrian hamster embryo cell transformation system.**Isfort RJ.**

Research Division, Procter & Gamble Pharmaceuticals, Cincinnati, Ohio 45206, USA. isfortrj@pg.com

The Syrian hamster embryo (SHE) cell transformation system has been used in investigational studies of basic mechanisms of neoplastic transformation, as well as in determining the carcinogenic potential of chemical, physical, and biological agents. Many of these investigations utilize an intermediate step in the SHE cell transformation process, known as morphological transformation, as an indicator of carcinogenicity. Cells that have acquired an increased potential to progress to malignancy, while the morphologically transformed phenotype is not completely understood, is thought to result from a block in the cellular differentiation of stem cells present within the cell population. In terms of determination of the transforming potential of biological/chemical/physical agents, more than 500 agents have been tested in the SHE cell transformation assay with an 80-90% correlation between MT and carcinogenic potential. As such, the SHE cell transformation assay has utility as a test to obtain short-term information on the carcinogenic potential of chemicals. One of the current interests with regard to SHE cell transformation assay utilization concerns the effect of growth and differentiation factors (GDFs). Analysis of the SHE cell transformation potential of the GDFs, epidermal growth factor (EGF), fibroblast growth factor (FGF-4), platelet-derived growth factor AA (PDGF AA), PDGF AB, PDGF BB, and transforming growth factor beta 1 (TGF-beta1), was conducted. All GDFs, with the exception of TGF-beta1, induced SHE cell transformation. An interesting difference between the GDFs was observed--PDGF A/B and FGF-4, but not PDGF A/A, EGF, or FGF-4, induced transformation after both a transient exposure and a continuous 7-day exposure, while continuous 7-day exposure was required for transformation by PDGF A/A, EGF, and FGF-4. Interestingly, transient 1-day and continuous 7-day TGF-beta1 exposure resulted in suppression of transformation induced by a variety of transforming agents including growth factors, Ames assay-positive carcinogens, Ames assay-negative carcinogens, and spontaneous transformation. Interestingly TGF-beta1 was not able to suppress transformation induced by the tumor promoter, TPA. Together, these data demonstrate the utility of the SHE cell transformation system for analyzing the transforming potential of agents and for characterizing differences in transforming mechanisms between different agents.

PMID: 11083101 [PubMed - indexed for MEDLINE]

□ 5: Expert Opin Investig Drugs 2000 Apr;9(4):747-64

Related Articles

Apoptosis modulators in the therapy of neurodegenerative disease

Deigner HP, Haberkorn U, Kinscherf R.

Anatomy and Cell Biology III University of Heidelberg, Germany.

Apoptosis is a prerequisite to model the developing nervous system. However, an increased rate of cell death in the adult nervous system underlies neurodegenerative disease and is a hallmark of multiple sclerosis (MS), Alzheimer's disease (AD), Parkinson's disease (PD) or Huntington's disease (HD). Cell surface receptors (e.g., CD95/APO-1/Fas receptor) and their ligands (CD95-L; TNF) as well as evolutionarily conserved mechanisms involving proteases, mitochondrial factors (e.g., Bcl-2-related proteins), reactive oxygen species, mitochondrial membrane potential, opening of the transition pore) or p53 participate in the modulation and execution of cell death. Effectors comprise oxidative stress, inflammatory processes, calcium toxicity, and survival factor deficiency. Therapeutic agents are being developed to interfere with these events, thus conferring the potential to be neuroprotective. In this context, drugs with anti-oxidative properties, e.g., flupirtine, N-acetylcysteine, idebenone, melatonin, and also novel dopamine agonists (ropinirole and pramipexole) have been shown to protect neuronal cells from apoptosis and thus have been suggested for treating neurodegenerative disorders like AD or PD. Other agents like non-steroidal anti-inflammatory drugs (NSAIDs) partly inhibit cyclooxygenase (COX) expression, thus having a positive influence on the clinical expression of AD. Distinct cytokines and growth factors and related drug candidates, e.g., nerve growth factor (NGF) and members of the transforming growth factor-beta (TGF-beta) superfamily, like growth differentiation factor 5 (GDF-5), are shown to protect tyrosine hydroxylase-positive dopaminergic neurones from apoptosis. Furthermore, peptidergic cerebrolysin is found to support the survival of neurones in vitro and in vivo. Treatment with protease inhibitors are suggested as potential targets to prevent DNA fragmentation in dopaminergic neurones of PD patients. Finally, CRIB (cellular replacement by immunisolation) is an auspicious gene therapeutic approach for AD. CRIB involves NGF secretion, which has been shown to protect cholinergic neurones from apoptosis when implanted in the brain. This review summarises and evaluates novel anti-apoptotic concepts and pharmacological intervention including gene therapy. Approaches currently being proposed or utilised to treat neurodegenerative disease are discussed.

Publication Types:

- Review
- Review, academic

PMID: 11060707 [PubMed - indexed for MEDLINE]

□ 6: Bone 2000 Sep;27(3):343-9

Related Articles



Femoral morphology and cross-sectional geometry of adult my

deficient mice.**Hamrick MW, McPherron AC, Lovejoy CO, Hudson J.**

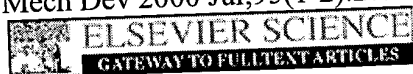
Department of Anthropology & School of Biomedical Sciences, Kent State
Kent, OH 44242, USA. mhamrick@kent.edu

GDF-8, also known as myostatin, is a member of the transforming growth factor (TGF-beta) superfamily of secreted growth and differentiation factors that regulate vertebrate skeletal muscle. Myostatin functions as a negative regulator of skeletal muscle growth and myostatin null mice show a doubling of muscle mass compared to control mice. We examined femoral morphology of adult myostatin-deficient mice to determine the effects of muscle fiber hypertrophy and hyperplasia on bone shape and cross-sectional geometry. Femora of age- and weight-matched adult mice homozygous for the myostatin null sequence were compared with those of wild-type controls (n = 8). Results show that, as was the case in previous studies, myostatin null mice have increased hindlimb muscle masses that are approximately double those of controls. Myostatin-deficient mice exhibit third trochanters that are significantly larger than those of controls, whereas the femoral midshafts of the control and experimental mice do not differ significantly from one another in cortical area, bending moment of inertia, or section modulus. Our findings indicate that the increased muscle mass of myostatin-deficient mice primarily affects sites of muscle insertion, but does not induce increased cortical bone deposition in the diaphysis relative to controls. We therefore conclude that the expanded third trochanters of myostatin-deficient subjects result from the increased Sharpey fiber expansion associated with muscle growth rather than cortical bone deposition in response to increased levels of mechanical stress.

PMID: 10962344 [PubMed - indexed for MEDLINE]

☐ 7: Mech Dev 2000 Jul;95(1-2):279-82

Related Articles, Nucleotide, Protein



Gdf16, a novel member of the growth/differentiation factor subfamily 13 of the TGF-beta superfamily, is expressed in the hindbrain and epibranchial placodes.

Vokes SA, Krieg PA.

Department of Cell Biology and Anatomy, University of Arizona Health Sciences Center, P.O. Box 245044, Tucson, AZ 85724, USA.

We have isolated and characterized the developmental expression of Xenopus laevis novel member of the growth/differentiation factor (gdf) gene family. The gdf16 gene encodes a pre-proprotein of 413 amino acids and a mature peptide of 122 amino acids. Gdf16 is most closely related to the zebrafish genes dynamo and radar, but has a completely different expression pattern. Gene expression is detected at early stages (stage 25) in the first two epibranchial placodes and in a hindbrain-specific placode. As development proceeds, the gene is expressed in all the epibranchial placodes.

hindbrain, and the diencephalon.

PMID: 10906478 [PubMed - indexed for MEDLINE]

☐ 8: *Vitr Mol Toxicol* 1999;12(3):133-148

Relate

Analysis of the Transforming Potential of Growth and Differentiation Factors in Syrian Hamster Embryo Cells: Reversible and Irreversible Transformation.

Isfort RJ, Cody DB, Kerckaert GA, LeBoeuf RA.

Corporate Professional & Regulatory Services, The Procter & Gamble Company, Valley Laboratories, Cincinnati, Ohio 45253-8707.

The mitogenic growth and differentiation factor (GDFs) oncostatin M (OM), epidermal growth factor (EGF), fibroblast growth factor 4 (FGF-4), platelet-derived growth factor AA (PDGF AA), PDGF AB, and PDGF BB and the anti-mitogenic GDF, transforming growth factor beta one (TGF-beta1), were tested in the 7-day continuous exposure and 24-h transient exposure Syrian hamster embryo (SHE) cell transformation assays to determine their reversible and irreversible transforming potential. OM was positive for morphological transformation (MT) while EGF, FGF-4, and PDGF AA were positive for statistically significant MT in the 7-day exposure SHE cell transformation assay. PDGF AB and PDGF BB (but not EGF, FGF-4, and PDGF AA) were positive for statistically significant MT in the 24-h transient exposure SHE cell transformation assays. TGF-beta1 was not only negative for the induction of MT in the 7-day exposure SHE cell transformation assays, but suppressed the spontaneous transformation response. Investigation of the transformation suppression by TGF-beta1 demonstrated that TGF-beta1 was able to irreversibly suppress the transformation potential of a variety of transforming agents including growth factor, Ames assay positive carcinogens, and Ames assay negative carcinogens. PDGF BB were investigated to better understand the reversible and irreversible transformation response. Differences in the receptors activated, the proteins phosphorylated by the receptors, and immediate early gene expressed were investigated in SHE cells treated with either PDGF AA or PDGF BB. Importantly, SHE cells treated with TGF-beta1 and PDGF BB, two GDFs, which modulate SHE cell transformation irreversibly, altered DNA methylation; PDGF AA did not demonstrate this effect. Together these data demonstrate that the SHE cell transformation assay can evaluate the transformation potential and mechanism of activation of GDFs.

PMID: 10894764 [PubMed - as supplied by publisher]

☐ 9: *Trends Endocrinol Metab* 2000 Jul;11(5):193-8

Related Articles

Full Text
on BioMedNet 

The role of the oocyte in folliculogenesis.

Erickson GF, Shimasaki S.

Department of Reproductive Medicine, University of California, San Diego
CA 92093-0674, USA. gerickson@ucsd.edu

Novel regulatory proteins have been identified within oocytes that are crucial in folliculogenesis. One of the most exciting oocyte signaling molecules is a member of the transforming growth factor beta (TGF-beta) superfamily, growth differentiation factor 9 (GDF-9). Loss-of-function studies have established GDF-9 as obligatory for proper folliculogenesis and fertility in female mice. The current goal is to understand how oocyte morphogens regulate folliculogenesis and how these actions and interactions are integrated into the overall processes of physiological pathophysiology. Who would have thought that oocyte morphogens would be so important for reproduction?

Publication Types:

- Review
- Review, tutorial

PMID: 10856922 [PubMed - indexed for MEDLINE]

☐ 10: Growth Factors 2000;17(4):269-85

Relate

Induction of endochondral bone formation by recombinant human transforming growth factor-beta2 in the baboon (*Papio ursinus*)

Ripamonti U, Crooks J, Matsaba T, Tasker J.

Bone Research Laboratory, Medical Research Council/University of the Witwatersrand Medical School, Johannesburg, South Africa. 177RIPA@chiron.wits.ac.za

Members of the transforming growth factor-beta (TGF-beta) superfamily, the bone morphogenetic and osteogenic proteins (BMPs/OPs) but not the TGF-beta 1 and 2 themselves, induce endochondral bone formation in vivo, when implanted at extraskeletal heterotopic sites of rodents. Here we show that recombinant human transforming growth factor-beta2 (hTGF-beta2) induces endochondral bone formation 30 days after implantation at heterotopic intramuscular sites of the baboon (*Papio ursinus*) at doses of 1, 5, 10, 25, and 50 microg per 100 mg of guanidinium-inactivated collagenous bone matrix as compared to control. By day 90 there was generation of large radiopaque and corticalized intramuscular bone. Five and 25 microg hTGF-beta2 induced large ossicles in the rectus abdominis muscle of the primate as evaluated by key parameters of bone formation, including general bone area, mineralized bone and osteoid volumes, and tissue alkaline phosphatase activity. By day 30 and 90 after healing, hTGF-beta2 also induced bone formation when implanted in the rectus abdominis in conjunction with a sintered porous hydroxyapatite. Northern blot analysis of mRNA expression in tissues from heterotopic specimens showed OP-1 (BMP-3) transcripts in low abundance and with a linear dose-dependent increase in the collagenous matrix and hydroxyapatite samples. Type IV collagen mRNA expression was also increased in the collagenous matrix and hydroxyapatite samples.

marker of angiogenesis, was stronger in collagenous than hydroxyapatite. Growth and differentiation factor-10 (GDF-10) mRNA transcripts were expressed in ossicles with a distinctly chondrogenic phase, but its expression was greater in porous hydroxyapatites, in which bone formation is not via a cartilage phase, but is rather intramembranous, without expression of type II collagen. In the same animals, however, 10 and 100 microg of the recombinant morphogen by identical carriers (collagenous matrix and sintered hydroxyapatite) failed to induce calvarial defects. Thus in the primate, TGF-betas themselves are inducers of endochondral bone formation, although the present data strongly indicate the inductive activity of hTGF-beta2 is site and tissue specific, since a single application of hTGF-beta2, or hTGF-beta1 in previously published experiments, did not induce calvarial defects, but did induce endochondral bone differentiation in heterotopic sites.

PMID: 10801076 [PubMed - indexed for MEDLINE]

11: Nat Genet 2000 Mar;24(3):262-5

Related Articles, OMIM



Regulation of left-right patterning in mice by growth/differentiation factor-1.

Rankin CT, Bunton T, Lawler AM, Lee SJ.

Department of Molecular Biology and Genetics, Baltimore, Maryland, USA

The transforming growth factor-beta (TGF-beta) superfamily encompasses a family of structurally related polypeptides that are capable of regulating cell growth and differentiation in a wide range of embryonic and adult tissues. Growth/differentiation factor-1 (Gdf-1, encoded by Gdf1) is a TGF-beta family member of unknown function that was originally isolated from an early mouse embryo cDNA library and expressed specifically in the nervous system in late-stage embryos and adult mice. Here we show that at early stages of mouse development, Gdf1 is expressed initially throughout the embryo proper and then most prominently in the primitive node, ventral neural tube, intermediate and lateral plate mesoderm. To examine its biological function, we generated a mouse line carrying a targeted mutation in Gdf1. Gdf1^{-/-} mice exhibit a spectrum of defects related to left-right axis formation, including visceral situs inversus, right pulmonary isomerism and a range of cardiac anomalies. In most Gdf1^{-/-} mice, the expression of Ebf1 (formerly lefty-1) in the left side of the floor plate and in the (formerly lefty-2), nodal and Pitx2 in the left lateral plate mesoderm was absent, suggesting that Gdf1 acts upstream of these genes either directly or indirectly to regulate their expression. Our findings suggest that Gdf1 acts early in the pathway of left-right activation that leads to the establishment of left-right asymmetry.

PMID: 10700179 [PubMed - indexed for MEDLINE]

12: J Reprod Fertil Suppl 1999;54:3-16

Related

Control of early ovarian follicular development.

McNatty KP, Heath DA, Lundy T, Fidler AE, Quirke L, O'Connell A, Groome N, Tisdall DJ.

Wallaceville Animal Research Centre, Upper Hutt, New Zealand.

Early follicular growth refers to the development of an ovarian follicle from primordial to early antral phase. In sheep and cows these phases of growth are classified by the configuration of granulosa cells in the largest cross-section of the follicle as types 1 (primordial), 1a (transitory), 2 (primary), 3 and 4 (preantral) (early antral). Follicles classified as type 1 may be highly variable within each phase with respect to number of granulosa cells and diameter of oocyte. Much of the variability in granulosa cell composition of type 1 follicles may occur at formation and account for the variability in granulosa cell composition throughout subsequent growth. There appear to be important differences among species (for example, cattle) in the number and function of granulosa cells relative to the diameter of the oocyte during the initiation of follicular growth. There is evidence that most of the growth phases from types 1 to 5 are gonadotrophin-independent and that they develop in a hierarchical manner. In sheep, cows and pigs, numerous growth factor receptor and gonadotrophin receptor mRNAs and peptides (for example, kit, stem cell factor, GDF-9, beta B and beta A activin/inhibin subunit, alpha subunit, follistatin, FGF-2, EGF, EGF-R, TGF beta 1,2 and 3 FSH-R and LH-R) are expressed in a phase of growth (for example types 1-5)-specific and cell-specific manner. However, the roles of many of these factors remain to be determined.

Publication Types:

- Review
- Review, tutorial

PMID: 10692841 [PubMed - indexed for MEDLINE]

☐ 13: Mol Cell Endocrinol 2000 Jan 25;159(1-2):1-5

Related Articles

Oocyte-expressed TGF-beta superfamily members in female ferrets.

Elvin JA, Yan C, Matzuk MM.

Department of Pathology, Baylor College of Medicine, Houston, TX 77030

Folliculogenesis is regulated by the interplay of extraovarian and intraovarian factors, and the importance of each type of regulation varies depending on the developmental stage of the follicle. Preantral follicle development is regulated predominantly by factors produced locally within the ovary and within the follicle itself. The oocyte is shown to produce soluble factor(s), which regulate a number of processes in follicle development, including cumulus expansion in the periovulatory period. Members of the TGF-beta superfamily are potent regulators of cell proliferation and differentiation.

number of organ systems, and three members, growth differentiation factor bone morphogenetic protein 15 (BMP-15) and BMP-6 are expressed by the may mediate effects attributed to the oocyte. Based on knockout mouse model does not play an essential role in ovarian function, but GDF-9 is absolutely preantral follicle development. GDF-9 also alters the periovulatory expression granulosa cell genes and stimulates cumulus expansion. Although BMP-15 identically to GDF-9, its role in regulating ovarian function is still unknown. This study examines the similarities and differences in sequence, expression, and function of oocyte-expressed TGFbeta family members with respect to regulating follicle

Publication Types:

- Review
- Review, tutorial

PMID: 10687846 [PubMed - indexed for MEDLINE]

☐ 14: Blood Cells Mol Dis 1999 Oct-Dec;25(5-6):310-23

Related Articles



Lineage-restricted expression of bone morphogenetic protein genes in human hematopoietic cell lines.

Detmer K, Steele TA, Shoop MA, Dannawi H.

Division of Basic Medical Sciences, Mercer University School of Medicine
31207, USA. detmer.k@gain.mercer.edu

To explore the possibility that bone morphogenetic proteins (BMPs) are autocrine/paracrine regulators of hematopoietic differentiation and function a panel of human cell lines encompassing the hematopoietic lineages for expression of members of this family of genes. Expression of BMP-2, BMP-4, BMP-6, BMP-7, BMP-9, and Growth and Differentiation Factor-1 (GDF-1), Placental Bone Morphogenetic Protein (PLAB), and Transforming Growth Factor-beta3 (TGF-beta3) was detected in various human cell lines. BMP-2, BMP-4, BMP-7, and TGF-beta3 expression was also detected in normal hematopoietic tissue. Expression of BMP-5 and BMP-8 was not detected. Restricted patterns of expression were found for BMP-4 (T-lymphoid), BMP-6 (lymphoid), PLAB (macrophage/monocyte), and GDF-1 (myeloid). Expression of BMP-2, GDF-1, and PLAB could be modulated by treatment with differentiating agents. Marked variations in the levels of BMP-4, BMP-7, and PLAB expression were encountered, indicating that disorders in BMP signaling pathways may play a role in the development of hematopoietic neoplasia. Copyright 1999 Academic Press.

PMID: 10660478 [PubMed - indexed for MEDLINE]

☐ 15: J Neurosci 2000 Dec 1;20(23):8597-603

Related Articles

Full text article at
www.jneurosci.org

Growth/differentiation factor-15/macrophage inhibitory cytokine-1, a novel trophic factor for midbrain dopaminergic neurons in vivo

Strelau J, Sullivan A, Bottner M, Lingor P, Falkenstein E, Suter-Crazz G, Galter D, Jaszai J, Kriegstein K, Unsicker K.

Neuroanatomy and Interdisciplinary Center for Neurosciences, University of Heidelberg, D-69120 Heidelberg, Germany.

Transforming growth factor-betas (TGF-betas) constitute an expanding family of multifunctional cytokines with prominent roles in development, cell proliferation, differentiation, and repair. We have cloned, expressed, and raised antibodies against a distant member of the TGF-betas, growth/differentiation factor-15 (GDF-15), which is identical to macrophage inhibitory cytokine-1 (MIC-1). GDF-15/MIC-1 mRNA and protein are widely distributed in the developing and adult CNS and peripheral systems, including choroid plexus and CSF. GDF-15/MIC-1 is a potent survival-promoting and protective factor for cultured and iron-intoxicated dopaminergic (DAergic) neurons cultured from the embryonic rat midbrain floor. The trophic effect of GDF-15/MIC-1 was not accompanied by an increase in cell proliferation and neuronal maturation, suggesting that GDF-15/MIC-1 probably acts directly on neurons. GDF-15/MIC-1 also protects 6-hydroxydopamine (6-OHDA)-lesioned nigrostriatal neurons in vivo. Unilateral injections of GDF-15/MIC-1 into the medial forebrain bundle just above the substantia nigra (SN) and into the left ventricle (20 micrograms) immediately before a 6-OHDA injection (8 microgram) prevented 6-OHDA-induced rotational behavior and significantly reduced losses of DAergic neurons in the striatum. Protection was evident for at least 1 month. Administration of 5 micrograms of GDF-15/MIC-1 in the same paradigm also provided significant neuroprotection. GDF-15/MIC-1 also promoted the serotonergic phenotype of cultured raphe neurons but did not support survival of rat motoneurons. Thus, GDF-15/MIC-1 is a novel neurotrophic factor with prominent effects on DAergic and serotonergic neurons. GDF-15/MIC-1 therefore has a potential for the treatment of Parkinson's disease and disorders of the serotonergic system.

PMID: 11102463 [PubMed - indexed for MEDLINE]

□ 16: Mol Cell Endocrinol 1999 Oct 25;156(1-2):189-93

Related Articles, Nucleotide

Localization of growth differentiation factor-9 (GDF-9) mRNA and protein in rat ovaries and cDNA cloning of rat GDF-9 and its rat homolog GDF-9B.

Jaatinen R, Laitinen MP, Vuojolainen K, Aaltonen J, Louhio H, Heikinheimo E, Ritvos O.

Department of Bacteriology and Immunology, Haartman Institute, University of Helsinki, Finland.

Although targeted gene disruption of GDF-9, an oocyte derived growth factor, causes an arrest of folliculogenesis and causes infertility in female mice, little is known about the expression of GDF-9 protein in the ovary. We show that GDF-9 protein is expressed in rat oocytes during folliculogenesis from the early primary follicle stage onwards. The most intensive immunostaining was seen in primary and preantral follicles. Analyses of the ontogeny of GDF-9 gene expression in postnatal rat ovaries show that the GDF-9 transcript levels are clearly increased on the second postnatal day, concomitant with the appearance of primary follicles. Interestingly, Northern blot hybridization analyses indicate a similar expression pattern for GDF-9, an ortholog of a mouse GDF-9 like factor for which we recently reported the protein amino acid sequence. The polypeptide sequences deduced from isolated ovarian cDNAs indicate that the rat GDF-9 prepropeptide is 440 amino acids (aa) in length. The putative mature peptide is 135 aa whereas rat GDF-9B is 391 aa long and the mature region is 125 aa. We conclude that (1) the GDF-9 protein is highly expressed in oocytes of primary follicles of rat ovaries suggesting that it plays a role in folliculogenesis and that (2) the full-length polypeptide sequence of GDF-9, a novel TGF-beta family member, is likely to be a secreted growth factor that regulates folliculogenesis at similar developmental stages as GDF-9.

PMID: 10612437 [PubMed - indexed for MEDLINE]

17: Gene 1999 Sep 3;237(1):105-11

Related Articles, Nucleotide, OMIM, Protein

Characterization of the rat, mouse, and human genes of growth/differentiation factor-15/macrophage inhibiting cytokine 15/MIC-1).

Bottner M, Laaff M, Schechinger B, Rappold G, Unsicker K, Suter-Cr

Department of Neuroanatomy, University of Heidelberg, Germany.
un691mb@genius.embnet.dkfz-heidelberg.de

We have isolated the rat, mouse and human genes of a distant member of the TGF-beta superfamily, growth/differentiation factor-15/macrophage inhibiting cytokine 15/MIC-1) by screening of genomic libraries. All three genes are composed of three exons, and contain one single intron that interrupts the coding sequences at positions within the prepro-domain of the corresponding proteins. The proteins contain the structural hallmarks of members of the TGF-beta superfamily, i.e. seven conserved carboxy-terminal cysteine residues that form the cystine knot. Orthologous molecules show the lowest sequence conservation of all members of the TGF-beta superfamily. RT-PCR reveals an abundant expression of GDF-15 mRNA in numerous embryonic and adult organs and tissues. Promoter analysis indicates the presence of multiple regulatory elements, including a TATA box sequence as well as several SP1, AP-1 and AP-2 sites. Deletion analysis suggests that a 350 bp region upstream of the start of the open reading frame appears to be

important for regulation of transcription.

PMID: 10524241 [PubMed - indexed for MEDLINE]

☐ 18: Genomics 1999 Aug 15;60(1):87-95

Related Articles, Nucleotide



Cloning, expression profile, and genomic organization of the m STAP/A170 gene.

Okazaki M, Ito S, Kawakita K, Takeshita S, Kawai S, Makishima F, O Kakinuma A.

Discovery Research Laboratories, Hoechst Marion Roussel Ltd., Kawagoe, Japan.

The preferential screening of cDNA libraries derived from the mouse osteoblast line MC3T3-E1 has yielded a cDNA clone encoding a 442-amino-acid protein designated STAP (signal transduction and adaptor protein), which contains motifs shared among transcription factors and adaptors such as a Zn-finger proline-rich domain, and a PEST sequence. The amino acid sequence homology also reveals that STAP is identical to a mouse oxidative stress protein, A170, with 90% homology with a human p62 protein that binds to the tyrosine kinase p60 domain. Northern blot analysis indicated a broad expression profile of STAP in various tissues and cell lines. In MC3T3-E1 cells, STAP mRNA was induced by treatment with TGF-beta, but not with BMP-2 or GDF-5. Analysis of the STAP gene isolated from the genomic library revealed that the STAP gene spans a region of over 11 kb and comprises eight exons. The transcription start site was identified by primer extension analysis to be located 35 bp upstream from the translation start site. Sequencing analysis of the 5' flanking region of the STAP gene revealed consensus motifs/sequences for several DNA binding transcription factors. The STAP gene had a TATA box, but no CCAAT box. Potential Sp1, AP-1, NF-E2, and NF-kappaB binding sites were found in the 5' flanking region (1.4 kb) of the STAP gene. Copyright 1999 Academic Press.

PMID: 10458914 [PubMed - indexed for MEDLINE]

☐ 19: Dev Biol 1999 Aug 1;212(1):68-79

Related Articles



Characterization of GDF-10 expression patterns and null mice

Zhao R, Lawler AM, Lee SJ.

Department of Molecular Biology and Genetics, Department of Gynecology and Obstetrics, Johns Hopkins University School of Medicine, 725 North Wolfe Street, Baltimore, MD 21205.

Baltimore, Maryland, 21205, USA.

Growth/differentiation factor-10 (GDF-10) is a TGF-beta family member homologous to bone morphogenetic protein-3. In order to determine the biological function of GDF-10, we carried out a detailed analysis of the expression pattern of GDF-10 and characterized GDF-10-null mice that we generated by gene targeting. During embryogenesis GDF-10 is expressed prominently in developing skeletal structures in the craniofacial region and in the vertebral column. In adult animals, GDF-10 is expressed at high levels in the brain, where GDF-10 is localized primarily to the Purkinje cell layer of the cerebellum, and in the uterus, where the expression of GDF-10 is regulated both during the menstrual cycle and during pregnancy. In contrast to high levels of GDF-10 expression in these tissues, we found no obvious abnormalities in GDF-10-knockout mice with respect to the development of these tissues. These results suggest either that GDF-10 plays no regulatory role in these tissues or that it is redundant with that of other growth factor-like molecules. Copyright 1999, Academic Press.

PMID: 10419686 [PubMed - indexed for MEDLINE]

☐ 20: Exp Cell Res 1999 Aug 1;250(2):351-63

Related Articles



p38 mitogen-activated protein kinase functionally contributes to chondrogenesis induced by growth/differentiation factor-5 in ATDC5 cells.

Nakamura K, Shirai T, Morishita S, Uchida S, Saeki-Miura K, Makishima H

Discovery Research Laboratories, Hoechst Marion Roussel Ltd., 3-2, Minamishinbuchi-cho, Kawagoe, Saitama, 350-1165, Japan.

Recent studies of intracellular signal transduction mechanisms for the transforming growth factor-beta (TGF-beta) superfamily have focused on Smad proteins, but have paid little attention to mitogen-activated protein (MAP) kinase cascades. Here we demonstrate that growth/differentiation factor-5 (GDF-5), but neither bone morphogenetic protein-2 (BMP-2) nor TGF-beta1, fully promotes the early chondrogenic response by inducing cellular condensation followed by cartilage formation in a mouse chondrogenic cell line, ATDC5. We investigated whether the three major types of MAP kinase play a functional role in the promotion of chondrogenesis induced by GDF-5. GDF-5 induced phosphorylation of p38 and extracellular signal-regulated kinase (ERK) but not that of c-Jun N-terminal kinase (JNK). The phosphorylation of p38 MAP kinase was also induced by BMP-2 and BMP-4. An inhibitor of p38 and p38 beta MAP kinase, SB202190, showed complete inhibition of cartilage nodule formation but failed to affect alkaline phosphatase activity induced by GDF-5. Expression of the type II collagen gene, a hallmark of chondrogenesis in vertebrates, was also induced by GDF-5 treatment and was suppressed by SB202190. On the other hand, although an inhibitor of MAP kinase, PD98059, inhibited the rapid phosphorylation of ERK by GDF-5, it inhibited

ALP activity nor cartilage nodule formation induced by GDF-5. These results suggest that the p38 MAP kinase cascade is involved in GDF-5 signaling and that a role of the p38 MAP kinase pathway is necessary over a longer period of chondrogenesis in ATDC5 cells. Copyright 1999 Academic Press.

PMID: 10413589 [PubMed - indexed for MEDLINE]

Display	Abstract	Sort	Save	Text	Add to Clipboard
Show: 20	Items 1-20 of 44			Page 1 of 3	Select

[Write to the Help Desk](#)
[NCBI](#) | [NLM](#) | [NIH](#)
[Department of Health & Human Services](#)
[Freedom of Information Act](#) | [Disclaimer](#)

spare-sun-solaris2.8